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# Motivations and Concerns of Patients With Access To Genetic Testing for Hereditary Pancreatitis

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**OBJECTIVES:** Direct DNA testing is now available for hereditary pancreatitis (HP). This study aimed to identify the factors that motivated individuals to participate in research and to determine how research participants used their genetic test results.

**METHODS:** A survey was mailed to 247 participants (110 male, 137 female) who were ≥18 yr of age and living in the US. Data analysis was primarily a description of frequency distribution of the responses.

**RESULTS:** Ninety-one of 247 participants (37%) completed the survey. Of the 55 female and 36 male respondents, 60% were 31–55 yr old, and a total of 54% tested positive for HP. The most common reason for participating in research was "to help a relative/family member" (61%), and genetic testing was pursued because of "the disturbance of seeing affected relatives" (48%) and "the desire to help future generations" (33%). Perceived risk of developing HP in the future was the least important motivating factor in seeking genetic testing. Sixty-two percent of respondents had received their genetic test results. All but one chose to share their results with at least one person: most often with family members (96%) and physicians (62%), and least often with insurance companies (4%). The most common influential factor in withholding information was "the fear of insurance discrimination" (23%).

**CONCLUSIONS:** The major motivations to participate in the HP genetic research study were to obtain genetic testing and to help current family members and future generations. The major concern was insurance discrimination. Participants clearly appreciate the availability of genetic testing for HP. These results suggest that a mechanism to disclose results to research participants should be considered, and effective ways to protect at-risk individuals from insurance discrimination must remain a genetics health care priority. (Am J Gastroenterol 2001;96:1610–1617. © 2001 by Am. Coll. of Gastroenterology)

## INTRODUCTION

Hereditary pancreatitis (HP) is defined as a chronic inflammatory disease of the pancreas present in multiple related family members in two or more generations. Data from over 200 HP kindreds worldwide demonstrate that HP is an autosomal dominant condition characterized by high but incomplete penetrance and variable expressivity (1, 2). HP is a relatively uncommon condition, most often diagnosed in Caucasians of European origin but also reported in a variety of ethnic and geographic populations.

To date, at least five mutations within the cationic trypsinogen gene on chromosome 7q35 have been reported to cause HP. The numbering system for these mutations now follows the recommendations for standardized nomenclature for human gene mutations rather than the chymotrypsinogen numbering system (Chy#) (3). The R122H mutation (Chy# R117H) and N29I mutation (Chy# N21I) seem to be the two most common mutations identified in HP kindreds (2, 4–7). In 1999, less common A16V, K23R, and 28delTCC mutations were reported (8–10). Only 65% of our HP kindreds can be attributed to these trypsinogen gene mutations, suggesting that additional mutations are still awaiting discovery (11, 12).

Although we are beginning to understand the impact of genetic testing on medical management for HP, little is known regarding the psychological impact on patients and their attitudes and behavior regarding the genetic testing process. To develop ethical guidelines for the use of genetic testing for HP and other inherited diseases, we first need to assess the issues of genetic testing as they apply to health providers, patients, and the patients' extended families. In this study, we sought to determine the issues that motivate and cause concern for patients obtaining genetic testing for HP.

## MATERIALS AND METHODS

A questionnaire-based research project was developed to examine issues of patient motivation and concern during the process of genetic testing for HP. The questionnaire and

**Table 1.** Possible Motivators for Participating in the Hereditary Pancreatitis Research Study

- To obtain genetic testing for cationic trypsinogen mutations
- To provide assistance or information for one's family
- To obtain medical advocacy such as a letter for employer/ insurance company
- To learn more about hereditary pancreatitis
- To contribute to the advancement of science
- Other reason

protocol for this study were approved by the institutional review board at the University of Pittsburgh.

The patient population was drawn from individuals participating in the Hereditary Pancreatitis research study, coordinated by the Midwest Multicenter Pancreatic Study Group. A total of 515 participants were recruited into this genetic research study between May, 1995 and November, 1998. All participants provided a blood sample for complete cationic trypsinogen mutation analysis and were offered the results of genetic testing after confirmation in a certified laboratory. Upon the participant's written request, test results were disclosed to the participant by telephone, with follow-up genetic counseling if requested. For the current study, we selected subjects who were enrolled in the HP study with informed consent before November, 1998, were at least 18 yr of age, and lived within the United States. Among the total of 515 HP study participants, 110 male and 137 female participants met these eligibility criteria.

A single self-administered questionnaire was designed to obtain information on patient demographics, perceptions of the risk and severity of HP, and the factors influencing their decision to seek genetic testing in a research study. Demographic information was collected to determine whether the respondents were representative of the entire HP research population. Perceived risk and severity of HP were measured to determine how severe or impacting HP is regarded by respondents. As illustrated by the Health Belief Model, perceived risk and severity of a medical condition are two factors that often influence human behavior when deciding to seek medical treatment (13). Additional questions were designed to identify patients' goals of genetic testing as well as how patients shared genetic information with doctors and relatives.

To identify the motivating factors to participate in a research study, we asked participants to select and rank the reasons they personally considered when deciding whether to enroll in the original HP research study. Participants were allowed to select as many motivating factors as they wished from a list of six (Table 1). The second question in this section assessed the importance of genetic testing as a reason to participate in the HP research study. Participants were instructed to rank five reasons for considering genetic testing as a motivating factor to participate in the HP research study (Table 2).

The survey also included questions addressing the use of genetic test results. Participants were asked to select factors that they personally considered when deciding to share or withhold information regarding their test results. Four common motivators and concerns were listed under two columns identified as "factors influencing the sharing of information" and "factors influencing the withholding of information" (Table 3). The last set of questions in this survey was designed to assess the types of relationships in which participants shared their test results (*e.g.*, relative, friend, physician, employer, insurance company).

**Table 2.** Possible Motivators Specific to Genetic Testing for HP

- The disturbing emotions prompted by witnessing a relative afflicted with HP
- To help one's future generations
- Pressure from relatives
- Presymptomatic screening to reduce uncertainty or anxiety
- Improvement of personal medical care

After pretesting and revising of the questionnaire, the surveys and instructions were mailed to the 247 selected individuals who met the eligibility criteria. To improve the response rate, a reminder letter was mailed to all participants approximately 1 month later. A unique identification number was issued to each survey in numerical sequence upon its return. Responses from surveys were entered into a computerized database (Microsoft Access 97) using a double entry and proofreading technique. Data analysis was primarily a description of frequency distributions of the responses. Statistical tests, $t$ tests, and $\chi^2$ tests were calculated using statistical software packages (SPSS version 8.0 [SPSS, Chicago, IL] and Excel version 5.0) to determine the significance of differences between frequencies.

## RESULTS

A response rate of 37% was obtained after mailing the survey and a follow-up reminder letter. Data analysis was performed using information collected from 91 participants (55 female, 36 male) (Table 4). The age of participants ranged from 19 to 74 yr, with the majority of participants falling within the 31–55 range. Most participants were married (76%), and 80% of participants reported having biological children. The average level of education of the respondents was representative of the US population, in

**Table 3.** Issues Regarding the Decision to Share or Withhold Genetic Information

Possible motivators for sharing information
- To contribute medical information to the family
- To equip a physician with information to improve medical care
- To seek advice or psychological support
- To strengthen relationship with family and/or friends

Possible concerns regarding sharing information
- Adverse emotional reactions from family
- Insurance genetic discrimination
- Employment genetic discrimination
- Information privacy

**Table 4.** Respondent Demographics

| | |
|---|---|
| Number of respondents | |
| Male | 36 (40%) |
| Female | 55 (60%) |
| Total | 91 (37%) |
| Age distribution (years) | |
| 19–20 | 1 (1%) |
| 21–30 | 14 (15%) |
| 31–40 | 22 (24%) |
| 41–50 | 20 (22%) |
| 51–50 | 17 (19%) |
| 61–70 | 11 (12%) |
| 70+ | 6 (7%) |
| HP disease status | |
| Affected | 48 (53%) |
| Unaffected | 41 (45%) |
| Unanswered | 2 (2%) |

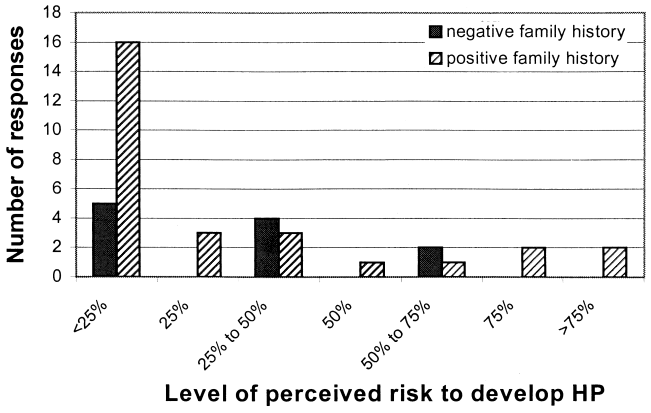


**Figure 1.** The association between family history of HP and the level of perceived risk of developing HP.

which approximately 80% of individuals ≥25 yr of age have completed 4 yr of high school or further education (14).

Respondents were categorized based on HP disease status. Forty-eight out of 89 participants (54%) reported receiving a diagnosis of HP based on medical history and/or a positive genetic test. The mean age (±SE) of symptom onset among the participants clinically diagnosed with HP was 15.4 (±2.0) yr.

The majority of participants reported having a positive family history of HP. Seventy-seven percent had at least one relative with a confirmed diagnosis of HP. Ten percent reported having relatives with "suspected HP." The remaining participants (13%) were the only individuals in their families who were affected with pancreatitis. In families with a confirmed history of HP, the average number of affected relatives in each family was seven. A family with this number of multiple affected relatives in subsequent generations follows the typical pattern of an autosomal dominant condition. In 36% of cases, these affected family members were either living in the same household or were a dependent of the participant.

Unaffected participants were asked to indicate their level of perceived risk for developing HP in the future on a scale from 0% to 100%. Thirty-nine unaffected participants reported an average level of perceived risk of 27%. The literature suggests that a positive family history of a genetic condition is also likely to be associated with perceived risk (15, 16). Therefore, we compared the level of perceived risk with the presence of a positive family history of HP. Interestingly, the majority of participants reported a perceived risk of <25% regardless of family history of HP (Fig. 1). There was no statistical difference in the level of perceived risk and family history of HP ($p$ value = 0.541). Moreover, perceived risk for developing HP was not statistically influenced by gender, age, or level of education.

The highest ranked reason for participating in the HP research study was "to help a relative/family member" (61%) (Table 5). The second highest ranked reason was "to obtain genetic testing" (13.5%), which was followed closely by a unique reason specified in the category "other reason" (12%). The reason that received the lowest ranking was "to obtain a letter/assistance for an employer/insurer" (0%).

The association between highly ranked motivators and other variables was investigated. Ten of the 12 individuals (83%) who ranked the motivator "to obtain genetic testing" as the most important motivating factor had a positive diagnosis of HP, suggesting that individuals who have already been clinically diagnosed with HP were highly motivated to participate in the HP research study for the purpose of confirming a clinical diagnosis through genetic testing. The majority of participants who ranked the motivator "to help a relative/family member" as the most important reason to participate were more likely to be married (80%), have living biological children (84%), and have a family history of HP (76%). Approximately one-half of the respondents who gave this motivator the highest ranking were not clinically affected with HP; thus, disease status did not seem to be associated with ranking this motivator as the most important reason to participate.

When asked to rank the most important motivating factor for specifically seeking genetic testing for HP, the most common response was the disturbing nature of "seeing relatives affected with hereditary pancreatitis" (48%). The second most important motivating factor was "to help my future generations" (33%). As before, the trends in ranking were associated with helping relatives and future generations.

Participants indicated the degree of importance of a series

**Table 5.** Reasons Ranked as "Most Important" in Participating in the HP Research Study

| Percentage of Respondents | Reason |
|---|---|
| 61% | "To help a relative/family member" |
| 13.5% | "To obtain genetic testing" |
| 12% | "Other reason" |
| 0% | "To obtain a letter/assistance for an employer/insurer" |

**Table 6.** Possible Motivators and Concerns Regarding the Decision to Request Genetic Test Results From a Research Study

| |
|---|
| Motivating statements: "Knowing test results . . ." |
| 1. ". . . will determine the cause of my illness." |
| 2. ". . . will prove there is a true medical reason to explain my symptoms." |
| 3. ". . . will determine the risk for my children to become affected with HP." |
| 4. ". . . will allow my doctor to monitor my future health more effectively." |
| 5. ". . . might bring my family closer together socially and emotionally." |
| 6. ". . . will reduce uncertainty/anxiety." |
| 7. ". . . will help me decide whether to have children or not." |
| Statements of concern: "Knowing test results . . ." |
| 8. ". . . might lead to medical insurance discrimination for my family or myself." |
| 9. ". . . might lead to employment discrimination in my current job or future jobs." |
| 10. ". . . might lead to feelings of 'survivor's guilt.'" |
| 11. ". . . might lead me to feel pressured to share information against my will." |
| 12. ". . . might draw my family apart socially and emotionally." |

of 12 statements regarding the motivators and concerns in requesting genetic test results. For all 12 statements, the frequency of responses was calculated for each of the three levels of importance: "not important," "somewhat important," and "very important" (Table 6). The benefit that received the highest level of importance was statement 3, "knowing my test results will determine the risk for my children to become affected with hereditary pancreatitis" (73%). Other benefits that received high levels of importance were statement 2, "knowing my test results will prove there is a true medical reason to explain my symptoms" (62%), and statement 4, "knowing my test results will allow my doctor to monitor my future health more effectively" (61%).

Among the statements that represented concerns about requesting genetic test results, participants indicated the highest level of importance for statement 8, "knowing my test results might lead to medical insurance discrimination for my family or myself" (22%). The majority of participants reported relatively low levels of importance for concerns such as employment discrimination and experiencing unpleasant reactions from other family members.

The association between levels of importance of these statements and other areas was also explored. One comparison studied the level of importance of statement 2, "to prove there is a true medical reason to explain symptoms," and the time lapse between onset of symptoms and the clinical diagnosis of HP. We hypothesized that participants who had a long time lapse between onset and diagnosis (≥5 yr) would report a higher level of importance of statement 2 when compared to participants who were diagnosed within 1 yr of symptom onset. Our data showed a statistically

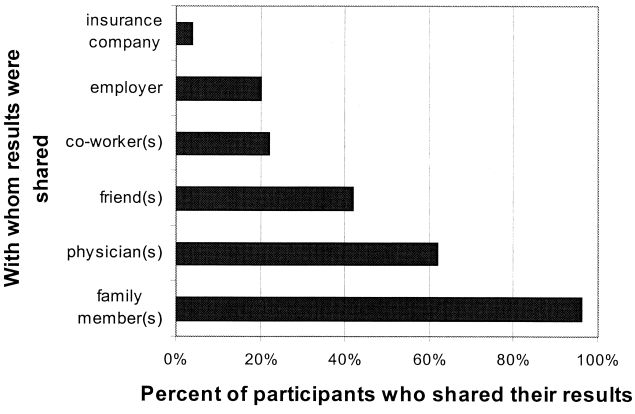


**Figure 2.** With whom HP genetic test results were shared.

significant association between high level of importance of statement 2 and a time lapse of ≥5 yr ($p = 0.033$).

Among responses from 91 participants, 62% of participants (35 female, 21 male) requested their HP genetic test results. Note that it is unknown whether the remaining 38% participants actively declined their genetic test results or were in the process of requesting this information. Participants who had already received their test results were asked to identify their motivators and concerns for sharing test results with a third party. The two most commonly selected factors that influenced the sharing of genetic information were "to give medical information to their family" (87%) and "to help improve my medical care" (76%). The most common concern regarding the decision to share genetic information was "the fear of insurance discrimination" (23%).

Ninety-eight percent of individuals who had received their results eventually shared their results with at least one person. Results were most commonly shared with a family member (96%) and a physician (62%). Participants were least likely to share results with their insurance companies (4%) (Fig. 2).

## DISCUSSION

With the recent availability of genetic testing for mutations in the cationic trypsinogen gene, the population affected with HP now faces complicated decisions regarding the choice to undergo genetic testing (17). In other heritable diseases for which there is direct genetic testing (*e.g.*, cystic fibrosis, sickle cell anemia), the issues that seem most strongly to influence patients' decisions to pursue genetic testing include severity of disease, mode of inheritance, family's experience with the disease, educational background, the beliefs of the chief organizer in the family, and the involvement and accessibility of research investigators (18). Other issues that also play a role include the age of the patient, age at onset of the disease, the benefits of knowing results, the threat to insurability, and rights of privacy (18). The presence and priority of these issues are likely to vary

**Table 7.** Potential Benefits, Risks, and Limitations of Genetic Testing for Hereditary Pancreatitis

| |
|---|
| Benefits |
| • To obtain a diagnostic confirmation of a hereditary etiology of pancreatitis |
| • To facilitate early diagnosis and treatment |
| • To identify individuals at increased risk for pancreatic cancer |
| • To obtain recurrence risk information for other relatives |
| • To reduce the uncertainty or anxiety of an at-risk individual |
| Risks |
| • May cause adverse psychological emotions such as grief, anger, denial, and alienation |
| • May have a lifelong psychological impact on descendants |
| • May lead to insurance and/or employment discrimination |
| • May stigmatize presymptomatic children who test positive |
| Limitations |
| • Testing may yield inconclusive results because additional HP genes and mutations are likely awaiting discovery |
| • The lack of a cure for HP may make an individual feel powerless or burdened |

considerably among patients and the type of disease involved.

Before undergoing genetic testing, patients and their referring physicians should consider the possible benefits, risks, and limitations of genetic testing (Table 7). From the medical provider's perspective, a key benefit of genetic testing is the diagnostic confirmation of a hereditary etiology of pancreatitis. For young patients with severe abdominal pain of unknown etiology, a genetic test may also be helpful in eliminating the need for lengthy, costly, and invasive medical evaluations. From the patients' perspective, a positive genetic test may provide validation of a physical cause of symptoms from a previously unrecognized or undiagnosed condition. A positive gene test also provides risk information to relatives of the index case (proband). These relatives can be referred for genetic counseling for presymptomatic genetic testing. In families with an identified trypsinogen gene mutation, individuals who receive negative test results are likely to find relief from the anxiety and uncertainty that accompany the fear of developing symptoms in the future. Individuals who presymptomatically test positive for an HP mutation can be identified early and may be candidates for strategies that prevent or control the development of clinical manifestation (4). Clinical trials to test such strategies are in development. Lastly, HP patients with prolonged chronic pancreatitis are known to have a 50-fold increased risk for pancreatic cancer over the general population (19); therefore, early identification of carrier status may increase medical surveillance and thereby facilitate earlier detection and minimize mortality due to pancreatic cancer. Furthermore, carriers can adopt lifestyle changes such as avoiding alcohol and smoking to minimize the increased risk of pancreatic cancer.

Although genetic testing conveys numerous benefits, the potential risks and limitations should be carefully outlined for a patient before genetic testing. Genetic information has an immediate effect on a patient's plan for health care, prognosis, and the perception of personal and family health. Powerful emotions such as anxiety, reassurance, guilt, and depression can accompany the process of genetic testing. In addition, genetic information has a powerful influence on an individual's reproductive behavior and a lifelong impact on future descendants (20, 21). Legal issues such as the potential for employment and insurance discrimination should also be considered (20, 22, 23).

One of the most important issues in the use of genetic testing is whether testing will lead to successful prevention or treatment of an inherited condition. For HP, recommended treatments and methods exist to control the pain associated with pancreatic attacks; however, there is no direct cure or method to prevent such attacks at this time. As seen in cases with Huntington's disease, presymptomatic patients may not recognize a justification for genetic testing if no cure for the disease is available. For these patients, genetic information may be a burden rather than a blessing.

As with many other heritable conditions, HP demonstrates genetic heterogeneity, meaning that HP can result from any one of several mutations in a number of possible genes. At this time, five mutations in a single gene have been recognized. However, the cause of pancreatitis in more than one-third of all HP kindreds cannot be explained by these five mutations in the cationic trypsinogen gene. It is unclear how many genes and mutations responsible for HP are still awaiting discovery. Therefore, genetic test results for this condition can often be confusing and difficult to interpret. For instance, unless a mutation has already been detected in a family, an individual with a negative test result still faces the possibility that he or she carries an as of yet undetectable mutation. Uninformative test results can aggravate the psychological state of a symptomatic patient as well as that of his/her relatives. In presymptomatic screening, positive test results may also be difficult to interpret because the genetic test cannot predict if and when pancreatic symptoms will develop. About one in five (20%) of mutation carriers will remain asymptomatic because of the reduced penetrance of the HP gene, and the factors controlling this are as yet unknown.

All of these potential risks, benefits, and limitations of genetic testing introduce complexity during the decision-making process to undergo genetic testing for any heritable condition. One of the goals of this survey study was to identify which risks and benefits are most influential to the HP research population.

In our HP research population we found that the decision to participate in the HP research study was most influenced by the desire to help a relative or family member and not by personal perceived risk of developing HP. Participants reported an average perceived risk for developing symptoms of pancreatitis of 27%. Is this perceived risk of 27% high or low? The interpretation of perceived risk is subjective and likely to differ among individuals. Although we cannot interpret this value, additional data from our survey strongly

suggest that perceived risk of developing HP was the least important reason when seeking genetic testing for HP. The majority of participants (48%) reported that the most important reason to seek HP genetic testing was the "disturbing nature of seeing relatives affected with HP," whereas an additional 33% felt that the most important reason for genetic testing was "to help my future generations." In fact, no participants listed "perceived risk of developing HP" among the top two reasons to seek genetic testing. Furthermore, "perceived risk of developing HP" was ranked by 58% respondents as the fourth most important reason to seek genetic testing among a list of five possible reasons.

When asked if "knowing test results will help me decide whether to have children or not," 85% participants reported that this statement was "not important" when deciding whether to request test results. Thus, reproductive decisions are not largely dependent on information gained from genetic testing of HP. This trend could be reflective of the fact that HP, though a debilitating disease, is not a lethal condition. However, some participants indicated that a family history or a clinical diagnosis of HP was enough to influence their reproductive behavior.

The data from this questionnaire suggest that approximately one-quarter of the participants requested their test results despite having a fear of insurance discrimination. The attitude regarding the decision to request test results was limited to the subset of family members who entered the study and obtained their test results. Although this represents a minority of eligible family members, their fear of insurance discrimination clearly reflects a major issue in health care.

The majority of participants (96%) reported that they shared their results with at least one family member. Approximately 62% shared their results with a physician, and approximately 42% shared their results with a friend. Not surprisingly, all of the participants who shared results with a friend or a physician also shared their results with a family member. There were no trends between gender and the decision to share test results; male and female participants were just as likely to share information with family, friends, and physicians. The high rate of sharing information among family and physicians also reinforces the hypothesis that the main motivator for participating in the HP research study was to seek information that would benefit one's family and personal medical care.

The data also support the hypothesis that participants are less likely to share information with insurance companies. In fact, only 4% of participants volunteered this information with their insurance companies. A significant number of participants shared their results with their employer (20%), suggesting that our research population is less concerned with the issue of employment discrimination.

Research studies offer a unique insight toward understanding aspects of research that affect participants both psychologically and behaviorally. We successfully identified the factors that are most important to people when deciding to participate in HP studies. Our data show that an overwhelming majority of individuals participated in the HP research study primarily to help their families and to obtain genetic testing for the purposes of helping current family members and future generations.

Second, we examined the factors that motivate and deter participants from sharing genetic test results. One of the most important factors that influenced participants to share results was the benefit of obtaining information that could potentially help relatives or future generations. The fear of discrimination from insurance companies was significant enough to suggest the need to educate the community regarding the laws that protect their rights while they seek genetic services.

Although this study generated some interesting and surprising results, there are several limitations of this retrospective study design. Survey critics indicate that a response rate of approximately $\geq$60% is generally sufficient to generate reliable data without response bias (24). Although the response rate of this study was only 37%, the demographics of the respondents are comparable to the HP research population that elected not to complete the questionnaire. Therefore, the 91 respondents may be representative of the demographics of the entire HP research population. It is unclear to what extent their knowledge and views represent the entire HP research population. The similarity in demographics between respondents and the remaining HP research population reduces response bias, but it cannot be eliminated. A second limitation is the lack of a standardized or validated survey tool. Although questionnaires have long since been used to study human behavior and attitudes, the questionnaire used in this study was tailored specifically for this special research population. Therefore, validity data for the distribution of responses will not be available until similar studies are conducted in the future.

Studies have been conducted to investigate the knowledge, attitudes, satisfaction, and/or the psychological state of patients undergoing testing for a familial pancreatic cancer, familial breast and ovarian cancer syndromes, and hemophilia (25–28). Brain *et al.* (28) found that patients undergoing familial breast cancer testing reported a personal vulnerability toward breast cancer. Tessaro *et al.* (26) reported that patients' major goals for breast cancer testing were to reduce uncertainty and assist with making future medical decisions, whereas the major disadvantages were related to the issues of confidentiality, genetic discrimination, and adverse psychological emotions such as stress. The current study appears to find similar concerns among the HP research population; however, this study appears to be the first of its kind to focus on this unique population and the rare condition of HP.

Currently, genetic testing is available on a clinical basis for HP and approximately 417 other single-gene disorders (29). As this list continues to grow, the concept of genetics is likely to impact many more people. It is clear from this survey study that genetic testing impacts not only the patient, but also his or her extended relatives.

The evidence that participants actively share genetic test results to improve their personal and family medical care illustrates the value of disclosing test results in a research setting. Clinical Laboratory Improvement Amendments of 1988 (CLIA) is a licensing procedure required of all laboratories that conduct testing on materials "derived from the human body for the purpose of providing information for the diagnosis, prevention or treatment of any disease or impairment of, or the assessment of the health of, human beings." The main function of the CLIA program is to expand regulation of laboratory testing and impose minimum requirements on laboratories to ensure the accuracy of testing. As such, research studies that implement genetic testing should follow a protocol that conforms to CLIA and genetic counseling guidelines so that participants and their referring physicians can maximize the benefits of genetic testing in a research setting (20, 30–35).

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